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Original Article (Pages: 6189-6194)

Cow's Milk Sensitization in Young Children with Gastroesophageal Reflux Disease

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Abstract

Background

Recent reports have suggested that gastroesophageal reflux disease (GERD) is link with cow's milk (CM) sensitization in children. The aim of this study was to determine the frequency of CM sensitization in young children with GERD.

Materials and Methods

This cross- sectional study included 33 children (median age, 2.93±1.90 years) with GERD according to a valid gastroesophageal reflux questionnaire, and 33 healthy children (median age, 3.39±1.90 years). CMA was diagnosed by skin test, serum specific immunoglobulin E level and atopy patch test to milk in both patient and control groups.

Results

Twenty-four children with GERD were positive for at least one of the diagnostic tests for CM sensitization compared to 13 children in control group (odds ratio [OR] = 1.78; 95% confidence interval [CI]: 1.14 to 2.80). Unlike the results of skin prick tests and specific Immunoglobulin E (IgE) levels to milk which showed no difference between children with GERD and healthy controls, there was a significant difference in the results of patch test (OR=2.06; CI95%: 1.46 to 2.91).

Conclusion

Based on our results, CM sensitization is 1.7 higher in children with GERD than non- GERD children. Patch testing preferably would better to perform for diagnosis of CM sensitization in those children with GERD.

Key Words: Children, Gastroesophageal reflux disease, Patch test**,** Milk allergy, Skin test.

*Please cite this article as: Moghtaderi M, Farjadian Sh, Hadi Imanieh M, Hosseini Teshnizi S. Cow's Milk Sensitization in Young Children with Gastroesophageal Reflux Disease. Int J Pediatr 2017; 5(12): 6189-94. DOI: **10.22038/ijp.2017.24825.2097**

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Received date: Jul. 15, 2017 ; Accepted date: Aug .22, 2017

1- INTRODUCTION

Gastroesophageal reflux disease (GERD) is usually caused by a failure of the lower esophageal sphincter and reverts of gastric content into the esophagus which affects children of all ages (1, 2). Gastroesophageal reflux is classified as physiologic and pathologic reflux or GERD, GERD is associated with symptoms such as, failure to thrive, feeding or sleeping problems, chronic respiratory disorders, esophagitis and apnea (3-5). For most of the typical GERD, history taking using a standard questionnaire (6) and physical examination is usually adequate to reach the diagnosis (7). Additional tests like contrast radiographic study, esophageal PH monitoring, endoscopy and intraluminal impedance can be helpful for diagnosis of GERD, too (8); empirical anti-reflux therapies, using a time- limited trial of high dose proton pump inhibitor, is a cost effective strategy for diagnosis of GERD (9) . Cow's milk allergy (CMA) is the most common food allergy among young children, because cow's milk represents the first foreign proteins introduced into infants' diet (10).

Children with CMA may manifest dermatological, gastrointestinal and respiratory symptoms (11). Immunoglobulin E- mediated and/or non-immunoglobulin E- mediated mechanisms may be implicated in hypersensitivity reaction to milk. The double- blind, placebo- controlled food challenge is usually considered as gold standard diagnostic test for CMA, however, it is time consuming, resource- intensive, and may induce anaphylaxis (12, 13). Thus alternative diagnostic tests like skin prick test (SPT), serum specific –immunoglobulin E (sIgE), and atopy patch test (APT) to milk are also suggested (14, 15). Both GERD and CM sensitization are common among gastrointestinal disturbances in infancy and childhood. There is some evidence that suggest a relationship between GERD and CM sensitization, because both have similar clinical presentation and their symptoms are often self- limited (16). This study was designed to identify the frequency of milk sensitization using skin prick test, serum specific –IgE and atopy patch test in young children with GERD.

2- MATERIALS AND METHODS

2-1. Study design and population

This cross-sectional study was performed on 33 children with GERD aged up to 6 years who referred to Namazee Allergy Clinic, affiliated with Shiraz University of Medical Sciences, Southwestern Iran, during 2016. GERD was defined using Infant Gastroesophageal Reflux Questionnaire I- GERQ (7) which was completed with the help of parent. Thirty- three unrelated healthy children with no history of symptoms for GERD and matched for age and gender were randomly selected as a control group among children referring to the orthopedic clinic.

2-2. Inclusion and exclusion criteria

Patients with esophageal atresia, anatomical malformation, children who were under treatment with antihistamines and medications with effect on lower esophageal sphincter were excluded.

2-3. Ethical consideration

After approval of the study protocol by the Ethics Committee of our university (ID number: EC-895100), informed consent was obtained from children's parents in both groups.

2-4. Questionnaire

Demographic information of children including age, gender, and family history of atopy was collected. A complete record of breast fed or fed a formula containing cow's milk was also obtained; each child

who fed at least for six months with breast was classified as exclusive breast feed.

2-5. Skin prick test

SPTs were done for all children with standard commercial extracts of milk (Greer, Lenoir, NC, USA). Histamine (10 mg/mL) and saline were used as positive and negative controls, respectively. The results of the skin tests were examined after 15 min and considered positive when the wheal was 3 mm greater in diameter than the negative control. Topical corticosteroids were stopped 1 day before the skin test. None of the patients was taking systemic corticosteroids.

2-6. Serum specific –IgE

Serum specific IgE (sIgE) levels to milk were measured with an enzyme-linked immunosorbent assay according to the manufacturers' instructions (Astra Biotech, Testkit Zur, Germany). Serum sIgE titers at levels ≥ 0.35 kAU/L were considered positive and were divided into 4 groups. Very low group had milk -specific IgE levels ranging from 0.36 to 0.71 kAU/ L; low group had milk specific IgE levels from 0.72 to 3.59 kAU/L; medium had IgE levels from 3.6 to 17.99 kAU/L; and high had specific IgE levels from ≥ 18.00 kAU/L based on the manufacturers' instructions and Sampson study (17) .

2-7. Atopy patch test

On the morning of the APT, 300 mg of milk powder was mixed with 0.2 ml of isotonic saline to make porridge and about 20 mg of this porridge using by Finn chamber (Epitest Ltd Oy Tuusula, Finland) on scanpor tapes was applied on the upper back of each children. Application sites were checked after 20 minutes for immediate reaction. The occlusion time of patch test was 48 hours. The evaluation was done 72 hours after attaching the patch tests. No reaction and redness without induration were regarded negative and redness with palpable induration was marked as positive reaction. All tests were prepared and applied by the same nurse and all reactions were classified by the expert allergist.

2-8. Data Analyses

Continuous variables were expressed as mean ± standard deviation (SD). Discrete variables were reported as frequency and percentage. Using t-test to compare mean of two groups, and Chi-square test to assess association between two categorical variables were done. Data was analyzed using SPSS 16.0 software, and $P < 0.05$ was considered statistically significant at 95% confidence interval (CI).

3- RESULTS

Thirty- three children with GERD (23 boys, 10 girls), aged 6 months to 6 years (mean age 2.93±1.90 years) and 33 healthy children (21 boys, 12 girls), aged 1 to 6 years (mean age 3.39±1.90 years) were included in the study. Twenty- four (73%) patients were positive to at least one of the diagnostic tests for CMA compared to 13 (39%) in control group (odds ratio [OR] = 1.78; 95%CI= 1.14 to 2.80).

The results of positive SPT to milk extract were five in children with GERD vs. one in control. ($p = 0.08$). There was no statistically significant difference between the two groups in the serum levels of sIgE to milk. The range of specific sIgE levels to milk in the patient and control groups are shown in **Table.1**.

Patch test was positive in 6 children with GERD, and none of control showed positive reaction (p= 0.01, OR=2.06; 95%CI= 1.46 to 2.91). Of five children with GERD and positive SPT, all showed low serum levels of sIgE to milk (0.72-3.59 kAU/L). Just one patient was simultaneously positive for SPT, APT and had 2.02 kAU/L sIgE to milk. None of the tested individuals show an irritation reaction after using APT.

The number of children with exclusive breast feeding was the same in both groups (23 children). Twenty- two patients (67%) had positive family history for atopy while four children (12%) in control group ($p<0.01$).

Table-1: Specific IgE levels to milk in children with GERD and healthy controls

Specific IgE levels to milk	Patients with GERD Number (%)	Control Number (%)
Very low (0.36-0.71 kAU/L)	3 (93%)	6 (18%)
Low (0.72-3.59 kAU/L)	9 (27%)	7 (21%)
Medium (3.60-17.99 kAU/L)	0	0
High (≥ 18.00 kAU/L)	0	0

GERD: Gastroesophageal reflux disease; IgE: Immunoglobulin E.

4- DISCUSSION

The purpose of this study was to determine whether the frequency of CMA was higher in young children with GERD. Current data indicate CMA is 1.7 higher in children with GERD than non- GERD children ($p = 0.005$). Prior research has found that the CMA was diagnosed in one third of the pediatric patients with signs and symptoms of GERD (16). Two other researches separately have reported a high prevalence of CMA (30% and 42%) in patients with GERD (18, 19). There are also some data which show the higher risk of CMA in children with GERD (20, 21).

Sensitization to milk has been shown by SPT and serum sIgE that these tests are considered as diagnostic tools for immediate type hypersensitivity reaction to milk. In this study, the results of SPT and sIgE to milk were mainly negative, so that non- IgE mediated reactions are thought to be responsible. In this regard, Korean children with silent GERD showed no difference with non-GERD based the presence of serum IgE to milk (22). However, it is also possible that SPT and sIgE not positive early in life (23). Non-IgE- mediated reactions to milk result from activation of other immunological pathways such as T- cell mediated responses, and APT has been reported as a diagnostic tool with high predictive capacity for late- phase allergic reaction (24). Moreover, APT is a valuable test in the diagnosis of food allergy in children with atopic dermatitis (25). Based on APT, our results showed twice high rate of CMA in patients with GERD than control. Cudowska and Kaczmarski showed that parallel SPT, sIgE and APT enhance the sensitivity to 92%, and specificity to 89% in diagnosis of GERD (26). Despite suggesting diagnostic tests, the current clinically valid method to demonstrate food allergy is still elimination and challenge with the suspected food (12). To prevent unnecessary milk elimination in children diet, Yukselen and Celtik (27), recently recommended a combination of oral food challenge and three previous mentioned tests for diagnosis of cow's milk allergy.

The results of this study showed that 39% of non- GERD children without CMA had high titers of sIgE. Similarly, a study showed high levels of sIgE in 25% of children without milk allergy (28). It is clear that high antibody titer is in favor for sensitization and having allergy need to development of allergy symptoms. In this study, family history of allergy was positive in 67% of the patients with GERD and 12% of the control. In contrast to this

result, Yuksel et al. (29) found that GERD was significantly more common in non-atopic children with asthma-like airway disease compared to the controls. Because CMA is one of the causes of GERD and this disease may form by other reasons which subsequently may lead to asthma-like manifestations even in non-atopic patients. In addition to small size of target group as the main limitation of our study, we did our diagnosis just using Infant Gastroesophageal Reflux Questionnaire I-GERQ (7), although it is a standard questionnaire, intraluminal impedance is more accurate. We also did not do open challenge or double-blind, placebo-controlled challenge for cow's milk for the detection of patients with milk allergy.

5- CONCLUSION

Based on our results, CM sensitization is 1.7 higher in children with GERD than non- GERD children. Patch testing preferably would better to perform for diagnosis of CM sensitization in those children with GERD.

6- CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

7- ACKNOWLEDGMENT

The authors declared that this study has received financial support by a grant from Shiraz University of Medical Sciences (ID number: 89-5100).

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